REMARKS

Claims 41-42, 44-46, 48-50, 56-57, 62-63, 65-66 and 68-73 are pending in this application. Claims 41-42, 44-46, 48-50, 55-57, 62-63, 65-66 and 68-73 were variously rejected under 35 U.S.C. §112, first paragraph. Claims 41-42, 44-46, 48-50, 55-57, 62-63, 65-66 and 68-73 were rejected under 35 U.S.C. §112, second paragraph. Claims 41-42, 44-46, 48-49, 65 and 68-73 were rejected under 35 U.S.C. §103.

By this amendment, claims 56, 57, 62, 63, 72 and 73 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification, for example, at page 4, lines 31-35.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

The Examiner continues to indicate that claim 55 is pending. Applicants respectfully point out that claim 55 was canceled with the Amendment submitted September 30, 2002.

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Written Description

Claims 56-57, 62-63, 66 and 70-73 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record. Applicants respectfully traverse this ground for rejection.

With regard to claim 66, the Examiner continues to assert that "the specification does not contemplate administering RPE that are allogeneic to the host." Office Action, page 3. Applicants respectfully submit that reference to "allograft" in the specification refers not only to the administered non-RPE cells with regard to the host mammal but also to the administered RPE cells with regard to the host mammal. Originally filed claim 12 depends from claim 7 and recites that the "transplantation is by allograft." Originally filed claim 7 depends from claims 1, 2 or 3 and recites that the "administering is by transplantation." Since original claim 1 is directed to administration of RPE only, the allograft of original claim 12 dependent from original claims 7 and 1 is the administered RPE cells, hence the RPE cells are allogeneic to the recipient host. Thus, the specification as originally filed describes an allograft transplantation of RPE cells, *i.e.*, administering RPE cells which are allogeneic to the host, as well as methods in which the non-RPE cells are allogeneic to the host.

The Examiner states that "the specification contemplates administering non-RPE that are allogeneic to the host using RPE cells provide immune privilege and increase survival time of the non-RPE in the host" but that "the specification does not contemplate administering RPE that are allogeneic to the host or to the non-RPE cells." Office Action, page 1.

From this statement, however, it is difficult to understand which RPE cells are acceptable from the Examiner's description of what is contemplated by the specification. If suggesting that the RPE cells are autologous to the non-RPE cells, when the non-RPE cells are allogeneic to the host (as contemplated), the RPE cells are also allogeneic to the host. If suggesting that the RPE cells are autologous to the host, when the non-RPE cells are allogeneic to the host, the RPE cells are also allogeneic to the non-RPE cells. In any case, this reasoning is not supported by the specification and the specification describes methods in which the RPE cells, as well as the non-RPE cells, are allogeneic to the host. Accordingly, claim 66 is in accordance with the written description requirement.

Applicants respectfully submit that pending claims 56, 62 and 72 are described in the specification as filed and do not contain new matter. Original claims 16 and 21 describe a pharmaceutical composition and an compartmentalized kit, respectively, which include RPE cells and cells that produce a therapeutic molecule (*i.e.*, non-RPE cells). As with claims 56, 62 and 72, claims 16 and 21 do not recite an allogeneic relationship between the RPE and the non-RPE cells. Thus, deletion of the previously added term "allogeneic" from the claims 56, 62 and 72 does not constitute adding new matter.

Although the Examiner states that original claims 16 and 21 "do not require non-RPE cells as claimed or that the non-RPE cells are insulin producing cells" (Office Action, page 2), as noted above, original claims 16 and 21 include RPE cells and cells that produce a therapeutic molecule (*i.e.*, non-RPE cells). The specification describes compositions comprising non-RPE cells which produce therapeutic proteins or biologically active molecules for use in treating diseases including metabolic diseases such as diabetes. Thus, original claims 16 and 21 included cells that produce a therapeutic molecule (*i.e.*, non-RPE cells) that were broader in scope than the pending claims 56, 62 and 72. However, the specification describes that the non-RPE cell can be an insulin

producing β-cell (page 4, lines 33-34) or pancreatic islet of Langerhans cell (original claim 22). Applicants respectfully submit that such a description in the specification conveys to one skilled in the art that the non-RPE cells of the claimed invention includes "insulin-producing cells."

The above not-withstanding, Applicants have amended claims 56, 57, 62, 63, 72 and 73 to recite "insulin-producing β cells" in the interest of expediting prosecution of this application.

In view of the foregoing, Applicants respectfully submit that the written description requirement has been met.

Enablement

Claims 41-42, 44-46, 48-50, 56-57, 62-63, 65-66 and 68-73 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

Applicants maintain that the specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention as claimed and is thus enabled. Applicants respectfully traverse the Examiner's assertion that insufficient guidance is provided and respectfully submit that a *prima facie* case of non-enablement has not been established.

The Examiner states that the specification is "enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal." Office Action, page 2. The Examiner also acknowledges that "non-RPE that produce a therapeutic protein had been administered into a host." Office Action, page 6.

Claims 56, 57, 62, 63 and 71-73 are directed to a pharmaceutical composition, a compartmentalized kit and an article of manufacture comprising RPE cells and non-RPE cells comprising insulin-producing β cells. Isolation and implantation of insulin-producing β cells was well known in the art at the time of filing,[1] and pharmaceutical reagents and containers for such compositions are described in the specification and also well known in the art. Thus, Applicants respectfully submit that claims 56, 57, 62, 63 and 71-73 are enabled by the specification, i.e., the specification teaches how to make and use the claimed composition, kit and article of manufacture.

The Examiner presents that transplantation of RPE cells was known at the time of filing[2], as was administration of non-RPE into mammals to produce therapeutic molecules. In support of the rejection, however, the Examiner states that "the art at the time of filing did not teach the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal, define the immune response to such a site or teach how to increase survival of allogeneic non-RPE in a mammal using RPE." Office Action, pages 3-4.

Claims 41-42, 44-46, 48-50, 65-66 and 68-70 are directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, where the non-RPE cells are allogeneic to the mammal. The RPE cells secrete FasL and are administered in an amount effective to create localized immunosuppression at the site of administration thereby increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal.

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[1] See, for example, Sigalla (1997), Weber (1997), Selawry (U.S. Pat. No. 5,725,854), of record.

[2] See, for example, Cherksey (U.S. Pat. No. 5,618,531), Ye (1993), of record. The Examiner continues to assert that "RPE were known to provide "immune privilege" (Ye of record, 1993 ... ." As presented in responses to previous Office Actions submitted September 30, 2002 and June 10, 2003, Applicants maintain that Ye does not teach the RPE cells provide immune privilege.

In the specification and in the responses to previous Office Actions,[3] Applicants present how it was known that FasL secreting Sertoli cells provided immune privilege site for co-implanted insulin producing cells. In response to this discussion, the Examiner states that the present "specification does not provide adequate correlation between Sertoli cells and RPE." In support of this position, the Examiner states that "the specification does not teach RPE secrete the same amount of FasL, that the structure of the site created by Sertoli cells and RPE is the same, that biological molecules secrete through a structure created by RPE or that the amount of secretion of a therapeutic protein obtained using RPE cells would be equivalent to that observed using Sertoli cells. Applicants submit that the request for these particular criteria is not sufficient to demonstrate lack of enablement and that these criteria are not necessary for enablement of the claimed invention.

With regard to the amount of FasL secreted by RPE cells, the specification demonstrates that RPE cells secrete substantial amounts of biologically active FasL. The bioassays show that it is at an amount sufficient to induce apoptosis in fetal thymocytes.[4] Given the teaching that RPE cells secrete biologically active FasL in easily measurable amounts, Applicants submit that the number of RPE cells needed to provide an immune privileged site and thus increase survival time of the non-RPE cells can be determined by the skilled artisan without undue experimentation. The specification provides guidelines for the number of RPE cells for administration and for ways of determining immune rejection, or cell survival, of the non-RPE cells.[5]

As noted, several times in the rejection the Examiner refers to "the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal" and that neither the specification nor the art teach the "structure" of such a site. The claimed invention relates to creating localized immunosuppression at the site of RPE and non-RPE cell administration. Neither

[3] See, for example, responses submitted September 30, 2002 and June 10, 2003.
[4] See, for example, specification page 16, lines 18-25, and pages 24-28.
[5] See, for example, specification page 15, lines 18-30.

the claims nor the specification discuss a requirement for a particular structure of the site, either to exist or to be formed. The Examiner's discussion regarding the structure of the site resulting from administration is not pertinent to the claimed invention, and any requirements regarding such a structure are not appropriate.

Although the Examiner refers to "unpredictability in the art," Applicants respectfully submit that the cited references and arguments put forth by the Examiner do not adequately support the lack of enablement rejection of the claimed invention. In fact, at page 9 of the Office Action, the Examiner states that the method of Cherksey increases "survival time" of the co-administered allogeneic glial cells "because RPE inherently secrete FasL causing an "immune privilege site."" Applicants again respectfully submit that the standard for determining an enabling disclosure is not limited to what is described in a particular example of the specification. In fact, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)*; M.P.E.P. § 2164.02.

Applicants submit that a *prima facie* case of non-enablement has not been established and that the specification provides sufficient guidance for one skilled in the art to make and use the invention as claimed.

Accordingly, the pending claims are in compliance with the enablement requirements.

Applicants respectfully point out an inconsistency by the Examiner with regard to the teaching of the specification. As noted above, at page 1 in the Office Action, the Examiner states that "the specification contemplates administering non-RPE that are allogeneic to the host using RPE cells provide immune privilege and increase survival time of the non-RPE in the host." Also,

at page 2 in the Office Action, the Examiner states that the specification is "enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal." However, as part of the enablement rejection at page 5 in the Office Action, the Examiner states that the "specification does not teach administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal." Clarification is requested.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 41-42, 44-46, 48-50, 56-57, 62-63, 65-66 and 68-73 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Although all of the pending claims are listed as rejected under 35 U.S.C. §112, second paragraph, the Examiner only discusses the rejection of claim 65. Claims 56, 57, 62, 63 and 70-73 are not dependent from claim 65 and the Examiner's discussion does not appear to relate to these claims. Although this point was also made in the response to the previous Office Action filed June 10, 2003, the Examiner did not address it in the present Office Action. Applicants can only assume that claims 56, 57, 62, 63 and 70-73 were listed in error and are not rejected under 35 U.S.C. §112, second paragraph. Accordingly, no further comment regarding these claims in this particular rejection is required.

In the rejection of claim 65, the Examiner states that the "phrase "facilitating survival of an allogeneic graft" has a different scope than "increasing survival time" of cells that are allogeneic to the mammal" and that it "appears that the preamble is intended to increase the survival time of all allogeneic cells that are administered to the host; however, the body of the claim only requires increasing the survival of the non-RPE cells." Office Action, page 8.

Applicants respectfully disagree with this assessment of the claim and submit that the pending claim language is not indefinite. The preamble of claim 65 states that the method is for "facilitating survival of an allogeneic graft of a population of non-RPE cells in a mammal." The claim preamble is clearly referring to "an allogeneic graft of a population of non-RPE cells" and not simply to all allogeneic cells administered. The body of the claim clearly states "increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal." Thus, contrary to the Examiner's assertion, both the preamble and this portion of the body of the claim refer to an or the "allogeneic graft of a population of non-RPE cells."

Applicants again respectfully submit that the use of "facilitating survival" in the preamble and of "increasing survival time" in the body of the claim does not render the claim indefinite. The claimed invention relates to the discovery that RPE cells secrete large quantities of FasL and thus can create a localized immunologically privileged site at the site of transplantation. The administering of a population of non-RPE cells to the site with the RPE cells increases the survival time of the non-RPE cells because of the localized immunosuppressive environment created by the RPE cells. Thus, claim 65 provides a method for facilitating survival of an allogeneic graft of a population of non-RPE cells through the presence of the RPE cells which create the immune privileged site. As stated in the body of the claim, the effectiveness of the method is measured with an increase in the survival time of the population of non-RPE cells in the mammal.

The Examiner also states that, with regard to claim 65, "it is unclear to what the survival time of the population of non-RPE cells is being compared" and asks "[i]s the survival time greater in the mammal than *in vitro*? greater in the mammal using RPE as compared to administering the non-RPE cells alone?" Office Action, page 8.

Applicants again point out that the claimed invention is directed to the use of RPE cells to create local immunosuppression to allow increased survival of co-transplanted, non-RPE cells as compared to survival of the non-RPE cells transplanted without the RPE cells. This is indicated, for example, in the following statements from pages 4 and 7 of the specification. "The method of the present invention may be used for enhancing the outcome of tissue transplants, by providing localized immunosuppression. That is, RPE cells may be used to facilitate transplant survival and graft function of the cells being transplanted." "The co-administering of RPE cells has the advantage in that the RPE cells create an immunologically privileged site thereby increasing the survival time of the co-administered cells." These statements make clear that the RPE cells increase survival of the co-administered non-RPE cells in the mammal, as opposed to survival of the non-RPE cells administered alone or survival of the non-RPE cells *in vitro*.

Thus, Applicants respectfully submit that claim 65, as well as dependent claims 41, 42, 44-46, 48-50, 66, 68 and 69, are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art. Accordingly, all of the pending claims are sufficiently definite.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 103

Claims 41-42, 44-46, 48-49, 65 and 68-73 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Cherksey (U.S. Patent 5,618,531). Applicants respectfully traverse this rejection.

As an initial matter, it is not clear which claims are rejected under 35 U.S.C. § 103(a). Claims 68-73 and claims 68-71 are listed as being rejected. Claims 56, 57, 62 and 63 are not listed as rejected, however, claims dependent from claim 56, claims 70 and 71, are rejected. To be fully responsive, the rejection of claims 41-42, 44-46, 48-49, 65 and 68-73 is addressed herein. Claims 56, 57, 62 and 63 are apparently free of the art and are not addressed in this section.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

Applicants respectfully submit that Cherksey does not support a *prima facie* case of obviousness with regard to the claimed invention.

As presented in the specification, the present invention is based on the discovery that retinal pigment epithelial (RPE) cells secrete an immunosuppressive cytokine, FasL, and can

thereby produce a localized immunosuppressive environment at the site of RPE cell implantation. The claimed invention is directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, wherein the non-RPE cells are allogeneic to the mammal. In the method, the RPE cells secrete FasL and are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells.

Cherksey describes implantation of a support matrix carrying cell types, neural or paraneural cells and glial cells, which are known to survive implantation into the brain, a known immune privileged site.[6] Cherksey does not teach or suggest the use of neural or paraneural cells to create an immune privileged site, much less the use of RPE cells to create local immunosuppression. Cherksey is also silent with regard to co-administration of RPE cell with insulin-producing β cells. Applicants respectfully submit that there is no motivation, in Cherksey or in the art, to modify the teachings of Cherksey to arrive at the claimed invention.

Cherksey is silent with regard to creation of an immune privileged site for the co-administered glial cells and with regard to the ability of RPE to create an immune privileged site through secretion of FasL. The Examiner states that "RPE cells inherently secrete FasL" and that "Cherksey need not teach the inherent feature of the RPE cells as claimed." Office Action, page 10. However, without recognition that RPE cells secrete FasL to create localized immunosuppression, there is no motivation for one to modify the teaching of Cherksey and specifically select RPE cells from the various neural and paraneural cells taught in Cherksey for use in the presently claimed invention, *i.e.*, a method in which RPE cells are used to create localized immunosuppression.

[6] See Cherksey, for example, column 8, line 65, through column 9, line 2.

The Federal Circuit states that a "retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. The critical inquiry is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness of making the combination" (original emphasis). That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Newell*, 891 F.2d 899, 13USPQ2d 1248 (Fed. Cir. 1989); *In re Spormann*, 363 F.2d 444, 448, 150USPQ 449, 452 (CCPA 1966).

Further, in *In re Sponnoble*, 405 F.2d 578, 160USPQ 237 (CCPA 1969), the court stated that it "should not be necessary for this court to point out that a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. The court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements."

The motivation for the use of RPE cells to create an immune privileged site is provided only by the Applicants in the specification. The Federal Circuit warns that "to imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher." *In re Zurko*, 111 F.3d 887, 42USPQ2d 1476 (Fed. Cir. 1997).

The Examiner states that Cherksey "does not teach co-administering RPE and non-RPE cells" but that "Cherksey suggests transplanting a matrix having both RPE and glial cells attached (column 9, line 2) and that the glial cells may be allogeneic to the host (column 11, line 37)." Office Action, page 9. Applicants respectfully disagree with this interpretation of Cherksey as a basis for the rejection.

At column 8, line 65 through column 9, line 6, Cherksey describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types." The reference Cherksey used to support the use of glial cells, Doering *et al.* (1984) *J. Neuro. Sci.* 63:183, described implantation of syngeneic glial cells. Cherksey does not mention whether or not the glial cells are allogeneic or not. At column 11, when Cherksey describes that cells useful in the methods of the invention may be allogeneic, there is specific mention of glial cells. Thus, Cherksey does not specifically teach that co-transplanted glial cells may be allogeneic to the recipient.

Further, the teachings of Cherksey would provide no expectation of success for the claimed invention since there is no teaching or suggestion that RPE cells can be used to create an immune privileged site. Nor is there any teaching or suggestion of transplantation outside of a pre-existing immune privileged site, the brain or spinal cord.[7]

Still further, Cherksey does not teach or suggest all of the claim limitations. As noted, Cherksey is silent with regard to co-administration of RPE cell with insulin-producing β cells.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

[7] See Streilein (1995, of record) for a list of immune privilege sites existing in the body.

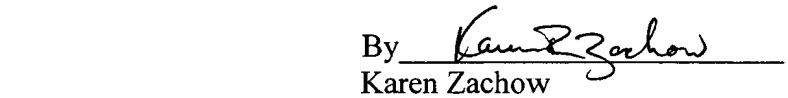
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500.

Dated: March 1, 2004

Respectfully submitted,

By 

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